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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,830	03/13/2002	Philip John Burke	ERD 100 CON	4061

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/099,830	BURKE ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,41-44 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34, 41-44 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

The Amendment filed on 10/26/2005 to the Non-Final Office Action of 07/26/2005 is acknowledged and has been entered.

Claims 34, 41-44 and 48 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The previous rejection has been withdrawn in view of Applicants arguments.

New Rejection:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34, 41-44 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedlos et al. #1 (Biochem. Pharmacol. 1992; 44: 1739-1743, IDS) in combination with Norris et al. (Can. J. Chem. 1977; 55: 1687-1695) in view of Friedlos et al. #2 (Biochemical Pharmacology 1992; 44: 25-31, IDS) and Jaiswal (J. Biol. Chem. 1994; 269; 14502-14508, IDS).

Friedlos et al. #1 teach a method of treating a human target cell to be destroyed (MAWI-human colon carcinoma, see Materials & Methods, page 1739) comprising administering CB1954 and nicotinamide riboside (reduced) (NRH) or an analogue thereof (NADH) which is able to permeate the target cell membrane. Friedlos et al. further teach that CB1954 is an exceptionally potent anti-tumor agent in-vivo capable of curing the rat Walker 256 carcinoma (1st paragraph, line

1), but CB-1954 has not been successful for the treatment of human tumors because of the relative inactivity of human DT diaphorase (NQO1) towards CB1954 (page 1739, 2nd paragraph). However, Friedlos et al. teach (page 1743, last paragraph) that such inactivity can be overcome by the addition of NADH resulting in enhanced cytotoxicity of CB1954 (see also abstract).

Friedlos et al. #1 do not explicitly teach a therapeutic system comprising a CB1954 and another reduced pyridinium derivative that are equivalents to the co-factors NRH or NADH in the reduction of CB1954 in a form for administration. Nor does Friedlos et al. teach that the prodrug is converted to a cytotoxic drug by the action of NQO2.

Norris et al. teach the identification and synthesis of pyridinium and dihydropyridine compounds which do not contain the adenine nucleotide portion of NADH (page 1687, 2nd column, 1st paragraph and Table 3). Specifically, the reference teaches a dihydropyridine compound consisting of 1-carbamoylmethyl-3-carbamoyl-1,4,-dihydropyridine (page 1688, 1st column (2i) and Table 3, i).

Friedlos et al #2. teach the identification of novel reduced pyridinium derivatives as synthetic co-factors in the reduction of CB 1954 by the enzyme DT Diaphorase (page 28, 1st column, last paragraph, and Table 1). Specifically, the reference teaches (page 28, 2nd column) that the actual structural requirements in a co-factor of DT diaphorase are fairly lax and, indeed, it would appear that there is little requirement for the adenine nucleotide portion of NAD(P)H at all. Thus, the simplest quaternary (and therefore reducible) derivative of nicotinamide, 1-methylnicotinaide, was as good of a co-factor as NAD(P)H.

Jaiswal teaches that the protein encoded by the NQO2 gene catalyzes 4-nitroreduction of the anti-tumor compound CB10-200, an analog of nitrophenylaziridine, with almost "equal efficiency" as the NQO1 protein (also known as DT-diaphorase) (page 14502, 2nd column, 1st and last paragraph and page 14503, 2nd column, 2nd paragraph).

(Note: Claims 34 and 42-44 as drawn to a compound of formula I or formula II, encompasses 1-carbamoylmethyl-3-carbamoyl-1,4,-dihydropyridine: With regards to Claim 34, R^1 is a substituted alkyl substituted by $CONH_2$, R^2 and R^3 are independenly H, and R^4 is H. With regards to claim 43, R is a substituted alkyl consisting of $CONH_2$. With regards to claim 43, the alkyl group is a C1 alkyl. With regards to claim 44, R is $-CH_2CONH_2$. Claim 41 is drawn to a compound of formula 1,

wherein the compound is 1-(carboxamidomethyl)-dihydronicotinamide which is another name for 1-carbamoylmethyl-3-carbamoyl-1,4,-dihydropyridine.)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute NRH (or NADH) employed by Friedlos et al. with an equivalent analogue of NRH (or NADH) such as 1-carbamoylmethyl-3-carbamoyl-1,4,-dihydropyridine. One would have been motivated to do so because as taught by Friedlos et al. #2, the actual structural requirements in a co-factor of DT diaphorase (NQO1) are fairly lax and, it would appear that there is little requirement for the adenine nucleotide portion of NAD(P)H. Thus, since it is well known in the art, as evidenced by Jaiswal, that the protein encoded by the NQO2 gene catalyzes 4-nitroreduction of CB10-200 with almost "equal efficiency" as the NQO1 protein and that CB1954 and CB10-200 are both nitrophenylaziridine prodrugs, one or ordinary skill in the art would have a reasonable expectation of success that the substitution of NRH (or NADH) with an equivalent analogue of NRH (or NADH) as taught by Norris et al. would achieve a series of co-factors for the 4-nitroreduction of CB 1954 by NQO2. Moreover, since it is well known in the art that CB-1954 is a potent anti-tumor agent in-vivo capable of curing rat Walker 256 carcinoma via the activity of NQO1 but is not effective in human because of the inactivity of NQO1. One would be motivated to generate a therapeutic system comprising the prodrug and an equivalent analogue of NRH (or NADH) in a form for administration because as evidenced by Friedlos et al., the relative inactivity of human DT diaphorase (NQO1) towards CB1954 can be overcome by the addition of NADH or NRH in human tumor cells. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by formulating a composition comprising CB1954 and an equivalent analogue of NRH (or NADH) such as 1-carbamoylmethyl-3-carbamoyl-1,4,-dihydropyridine for administration, one would achieve a "pharmaceutical" composition that can be used for the treatment of cancer.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER